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Myocardial Scars More Frequent Than Expected

Magnetic Resonance Imaging Detects Potential Risk Group

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OBJECTIVES The aim of this study was to investigate the prevalence of clinically recognized myocardial infarctions (RMIs) and unrecognized myocardial infarctions (UMIs) in 70-year-old subjects, assessed with magnetic resonance imaging (MRI), and to relate the findings to cardiac function and morbidity.

BACKGROUND Late enhancement MRI identifies myocardial scars and thereby has the potential to detect UMI.

METHODS Cardiac MRI was performed on 259 randomly chosen 70-year-old subjects. Late enhancement and cine sequences were acquired, and the ejection fraction and left ventricular (LV) mass were calculated. Late enhancement involving the subendocardial layer was considered to represent myocardial infarction (MI) scars, and their volumes were calculated. Information on cardiac morbidity and risk factors was collected from medical records and from a health examination. Subjects with MI scars, with or without a hospital diagnosis of MI were classified as RMI or UMI, respectively.

RESULTS The images from 248 subjects (123 women, 125 men) were assessable. Myocardial infarction scars were found in 60 subjects (24.2%), in 49 of whom (19.8%) they were UMIs. The volumes of the UMIs were significantly smaller than those of the RMIs. There was an increased frequency of chest pain symptoms among the subjects with UMI or RMI compared with those without MI scars. Ejection fraction was significantly lower and LV mass significantly larger in the subjects with UMI or RMI than in those without MI scars.

CONCLUSIONS Unrecognized MI detected with MRI was more frequent than expected in 70-year-old subjects. The subjects displaying these UMIs may represent a previously unknown potential risk group for future cardiovascular events. (J Am Coll Cardiol 2006;48:765–71) © 2006 by the American College of Cardiology Foundation

Until recently, the primary tool for estimating the prevalence and prognosis of clinically unrecognized myocardial infarction (UMI) has been detection of Q waves on electrocardiography (ECG) (1,2). Using this method, UMI has been estimated to constitute at least one-fourth of all myocardial infarctions (MIs) (1,2), and the prevalence is said to increase with age, approximately 10% per year (3). The true prevalence of UMI, however, remains unknown, because not all MIs result in persistent Q waves (4).

Unrecognized MI, with persistent Q waves, signifies a considerable health risk, as indicated by the fact that affected persons have risk factor profiles and mortality rates similar to those in persons with recognized myocardial infarction (RMI) (2).

Myocardial enhancement that is present on magnetic resonance imaging (MRI) when the intravascular concentration of gadolinium contrast is declining is referred to as late enhancement. Late enhancement MRI accurately detects MIs and other myocardial scars as hyperintense areas (5–7). As late enhancement MRI detects not only Q-wave MIs but also non–Q-wave MIs (7), this technique may reveal an even greater prevalence of UMI than has previously been estimated. The aim of this study was to investigate the prevalence of RMI and UMI in a population-based sample of 70-year-old subjects, assessed with MRI, and to relate the findings to cardiac function and morbidity.

METHODS

Study population. After approval from the ethical committee, cardiac MRI was performed on an unselected subsample from the PIVUS (Prospective Investigation of the Vasculature in Uppsala Seniors) study (8).

Eligible for the PIVUS study were all subjects aged 70 years and resident in the municipality of Uppsala, Sweden. The subjects were chosen in a randomized manner from the register of municipality inhabitants, and 2,025 subjects were invited to participate within weeks from their 70th birthday; 1,016 agreed and gave written informed consent (Fig. 1).

From the original cohort, 283 subjects were consecutively invited to undergo cardiac MRI, which was finally performed on 259 subjects, with a mean delay of 16 months (range 3 to 22 months) from the primary investigations. The number of subjects invited was determined by the availabil-

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Abbreviations and Acronyms

CHF = congestive heart failure
EF = ejection fraction
LV = left ventricle/ventricular
MI = myocardial infarction
MRA = magnetic resonance angiography
MRI = magnetic resonance imaging
PIVUS = Prospective Investigation of the Vasculature in Uppsala Seniors study
RMI = recognized myocardial infarction
UMI = unrecognized myocardial infarction

ity of MRI scan time, financial limitations, and the ambition that the interval between the primary investigations and the MRI examination should not be too long. Eleven examinations were not assessable because of poor quality, leaving assessable data from 248 subjects (123 women, 125 men) (Fig. 1).

The basic characteristics and major cardiovascular risk factors among these subjects (Table 1) did not differ significantly from those in the entire PIVUS study population (8) except that there were fewer current smokers in the subjects of the present study (7.7% compared with 11%). The cardiac morbidity of the participants in the PIVUS study did not differ from that of the background population (8).

Subject data. Participants in the PIVUS study answered a questionnaire about their medical and drug histories. Furthermore, medical records from Uppsala University Hospital were searched retrospectively for cardiovascular diagnoses. Of the 248 subjects with assessable late enhancement MRIs, 157 had been treated at the hospital, and their medical records were scrutinized (C.E.B.). Two subjects reported in the questionnaire that they had been treated for MIs at other hospitals. Their medical records were retrieved and studied (C.E.B.). Subjects with a hospital diagnosis of MI were considered to have had a clinical MI and are hereafter referred to by that term. The hospital diagnosis of MI was set using the World Health Organization criteria before the year 2000 (n = 4) and the criteria defined by the Joint European Society of Cardiology/American College of Cardiology Committee thereafter (n = 7) (9).

Table 1. Basic Characteristics and Major Cardiovascular Risk Factors

	Study Population (n = 248) Mean (SD)
Female gender, %	49.6
Height, cm	169 (9.1)
Weight, kg	77 (13)
Waist circumference, cm	91 (10)
Body mass index, kg/m^2	26.9 (4.0)
Waist/hip ratio	0.90 (0.065)
Systolic blood pressure, mm Hg	150 (22)
Diastolic blood pressure, mm Hg	79 (9)
Heart rate, beats/min	61 (8.6)
Serum cholesterol, mmol/l	5.4 (0.94)
LDL cholesterol, mmol/l	3.4 (0.83)
HDL cholesterol, mmol/l	1.5 (0.37)
Serum triglycerides, mmol/l	1.3 (0.65)
Fasting blood glucose, mmol/l	5.3 (1.5)
Hypertension, %	73.0
Hypercholesterolemia, %	54.4
Diabetes, %	12.5
Current smoking, %	7.7

HDL = high-density lipoprotein; LDL = low-density lipoprotein.

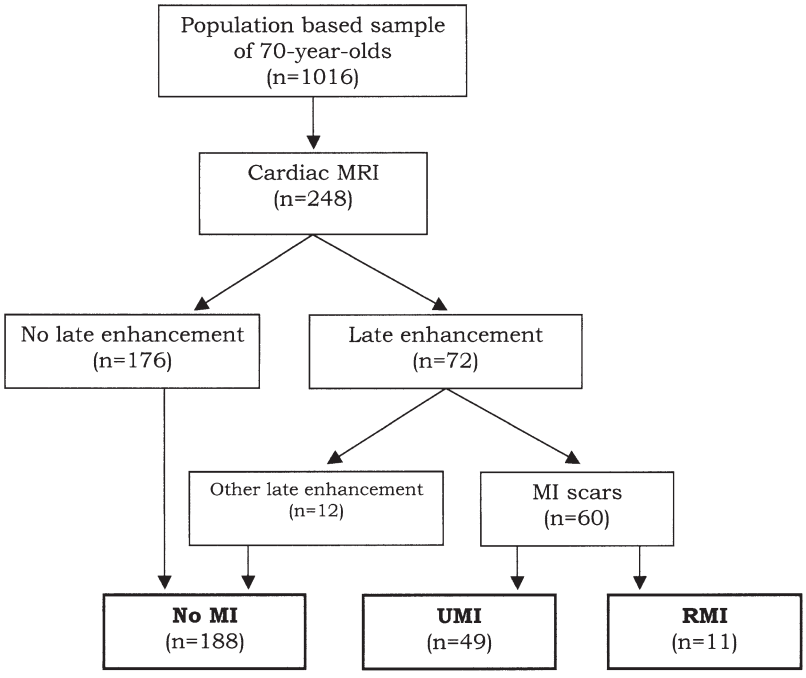

Figure 1. Groups were formed from the population-based sample of 70-year-old subjects. MRI = magnetic resonance imaging; No MI = no myocardial infarction scar; RMI = recognized myocardial infarction (i.e., MI scar in combination with MI diagnosis in medical records); UMI = unrecognized myocardial infarction.

Subjects lacking medical records and who did not report MI in the questionnaire were regarded as not having had a clinical MI (n = 88). One subject reported having been treated for an MI at Uppsala University Hospital, but had no medical record there and was regarded as not having had any clinical MI.

In the PIVUS study, blood pressure, fasting blood glucose, low-density lipoprotein cholesterol, and 12-lead ECG were measured using standard techniques (8). The following definitions were applied: hypertension = blood pressure ≥140/90 mm Hg or antihypertensive treatment; diabetes = fasting blood glucose ≥6.2 mmol/l or antidiabetic treatment; hypercholesterolemia = low-density lipoprotein cholesterol ≥3.5 mmol/l or lipid-lowering treatment; Q-wave on ECG = Minnesota codes 1:1 or 1:2 (10).

The data on cardiac morbidity of the subjects (Table 2) were taken from the medical records. The term "other cardiac diagnoses" includes atrial fibrillation, other arrhythmias, congestive heart failure (CHF), and valvular disorders.

Image acquisition. Imaging was performed on a 1.5-T MRI system (Gyroscan Intera, Philips Medical Systems, Best, the Netherlands) with a 25 mT/m gradient system, using the standard SENSE cardiac coil (Philips Medical Systems) in the supine position and retrospectively gated vector ECG for cardiac triggering.

After injection of 40 ml Gd-DTPA-BMA (Omniscan, GE Healthcare, Oslo, Norway), the subjects were initially submitted to whole body magnetic resonance angiography (MRA), after which late enhancement images were acquired using a 3-dimensional inversion recovery gradient echo sequence covering the entire heart in short- and long-axis views. The acquired slice thickness was 10 mm with a resolution of 1.56 × 2.81 mm. The inversion time was individually adjusted to null viable myocardium for every subject. The mean post-contrast time was 33.7 min, ranging from 25 to 64 min.

Cine images were acquired during breath holding using a steady state free precession sequence covering the left ventricular (LV) myocardium from the apex to the atria in 8-mm-thick short-axis slices with a 2.5-mm slice gap, an acquired in-plane resolution of 2.27 × 1.81 mm, and 18 phases recorded per cardiac cycle. Two slices were acquired per breath hold. The temporal resolution varied between the subjects depending on their heart rates.

Image analysis. For assessment of the late enhancement images, a PACS workstation (Impax, Agfa, Mortsel, Belgium) was used by 2 observers (C.E.B. and T.B.) independently and in a consensus reading. The observers were blinded to information on any previous disease.

Left ventricular myocardium nulled by the inversion pulse was visually assessed as viable, whereas LV myocardium showing late enhancement (i.e., hyperintense myocardium) was classified as nonviable. To classify myocardium as nonviable, late enhancement had to be visible in short- as well as long-axis images, when long-axis images were available (n = 243 of 259). The areas showing late enhancement were classified, by the same 2 observers in consensus, into 4 groups according to their distribution: transmural, subendocardial, located in the mitral valve insertion area, or presenting another distribution. Late enhancement that involved the subendocardial layer was considered to represent an MI scar (11,12) (Fig. 1) and is hereafter referred to by that term.

The LV function was assessed (C.E.B.) on a workstation with commercially available analysis software. Quantification was performed on short-axis images, using a semiautomatic method with papillary muscles included in the LV mass. Ejection fraction (EF) and LV end-diastolic mass were computed assuming a myocardial density of 1.05 g/ml (13). The LV mass was adjusted for body surface area (14).

The myocardium displaying late enhancement was manually outlined (C.E.B.). The volumes of the enhanced myocardium were calculated in grams and in percent of the LV mass. The location of late enhancement was classified (C.E.B. and T.B. in consensus) in accordance with the American Heart Association segmentation (15).

Table 2. Cardiac Morbidity and Major Cardiovascular Risk Factors in Relation to Presence of MI Scars and Clinical MI

			MI Scars (n = 60)			
	No MI Scars (n = 188)	No MI vs. UMI	UMI (n = 49)	UMI vs. RMI	RMI (n = 11)	RMI vs. No MI
Cardiac morbidity						
Diagnosed angina	7 (3.7%)	NS	3 (6.1%)	*	5 (45.5%)	*
Chest pain symptoms	25 (13.3%)	*	14 (28.6%)	*	11 (100%)	*
Other cardiac diagnosis	12 (6.4%)	*	9 (18.3%)	NS	2 (18.2%)	*
PCI/CABG	3 (1.6%)	NS	2 (4.1%)	*	7 (63.6%)	*
Findings						
Pathological ECG Q-wave	7 (3.7%)	NS	3 (6.1%)	*	5 (45.5%)	*
Risk factors						
Hypertension	137 (72.9%)	NS	35 (71.4%)	NS	9 (81.8%)	*
Hypercholesterolemia	103 (54.8%)	NS	25 (51.0%)	NS	7 (63.6%)	*
Diabetes	19 (10.1%)	NS	8 (16.3%)	NS	4 (36.4%)	*
Current smoking	13 (6.9%)	NS	4 (8.2%)	NS	2 (18.2%)	NS

*$p < 0.0167$, i.e., 0.05 with Bonferroni correction.

CABG = coronary artery bypass graft surgery; MI = myocardial infarction; No MI = no MI scar; PCI = percutaneous coronary intervention; RMI = recognized myocardial infarction, i.e., MI scar in combination with MI diagnosis in medical records; UMI = unrecognized myocardial infarction.

Three groups were formed: subjects without MI scars (no MI); subjects with an MI scar but no clinical MI (i.e., a UMI); and subjects with both an MI scar and clinical MI (i.e., an RMI) (Fig. 1). The interobserver variability of the last consecutive 201 late enhancement assessments was determined.

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agree to the manuscript as written.

Statistical analysis. StatView 5.0.1 (SAS Institute, Cary, North Carolina) was used for statistical analyses. For estimating differences between groups, the chi-square test and Bonferroni correction were used. Analyses of variance of infarct size, EF, and LV mass were made using ANOVA, with Bonferroni correction for post-hoc analysis. The significance level was set at 0.05 in all analyses.

RESULTS

Late enhancement was found in 72 (29%) of the 248 subjects (Fig. 1). In 1 of these, only short-axis images were available. In 39 of the 248 subjects (15.7%), the late enhancement was transmural, in 21 (8.5%) it was subendocardial, in 5 (2%) it was located mid-wall in the mitral insertion area, and in 7 (2.8%) it showed another distribution (4 mid-wall and 3 subepicardial).

Myocardial infarction scars were found in 60 of the 248 subjects (24.2%) (Fig. 1); 24 of these were women and 36 were men. None of the subjects displaying late enhancement had a diagnosis of myocarditis, sarcoidosis, amyloidosis, or dilated or hypertrophic cardiomyopathy in their medical records before MRI.

The subjects with RMI constituted 4.4% (11 of 248), whereas 19.8% (49 of 248) had UMIs (Figs. 1 and 2). There were more women in the UMI group, 45% (n = 22 of 49), than in the group with RMIs, 18% (n = 2 of 11). Two subjects (men) had clinical MI, but were not assessed as having any MI scar in the consensus reading. Three of the 49 subjects with UMI and 7 of the 188 without MI scars had a pathological Q-wave on ECG (Table 2). Unrecognized MIs were more frequently located in the inferior and inferolateral segments (15) of the LV, whereas RMIs seemed to be more evenly distributed between the segments (Fig. 3).

The volumes of the UMIs were significantly smaller than those of the RMIs. Two subjects in the RMI group lacked cine images and, hence, a value of LV mass, and, therefore, the volumes could not be calculated in percent for these 2 subjects. The difference was significant, however, both when the volumes were calculated in grams (UMI mean 2.5 g, range 0.11 to 21.7 g; RMI mean 9.3 g, range 0.20 to 26.9 g) and in percent (UMI mean 1.9% of LV mass, range 0.12% to 9.6%; RMI mean 4.8% of LV mass, range 0.35% to 13.2%).

The cardiac morbidity and major cardiovascular risk factors of the subjects without MI scars, with UMI, and with RMI are presented in Table 2. Cardiac morbidity was more frequent among the subjects with UMI or RMI than in those without MI scars. Of the subjects with other cardiac diagnoses in the UMI group, 1 had atrial fibrillation, 4 had other arrhythmias, 2 had CHF, and 2 had a valvular disorder. In the RMI group, 1 had atrial fibrillation and 1 had CHF. The UMI group and the RMI group did not differ in the frequency of these diagnoses (Table 2). The prevalence of hypertension, hypercholesterolemia, and diabetes was increased in the subjects with RMI compared with those without MI scars (Table 2).

Ejection fraction was significantly higher among the subjects without MI scars than among those with UMI or RMI (Fig. 4). Left ventricular mass was significantly larger in the subjects with UMI than in those without MI scars and even larger in those with RMI (Fig. 4).

There was an interobserver agreement of 74% in the late enhancement assessments. The agreement between observer

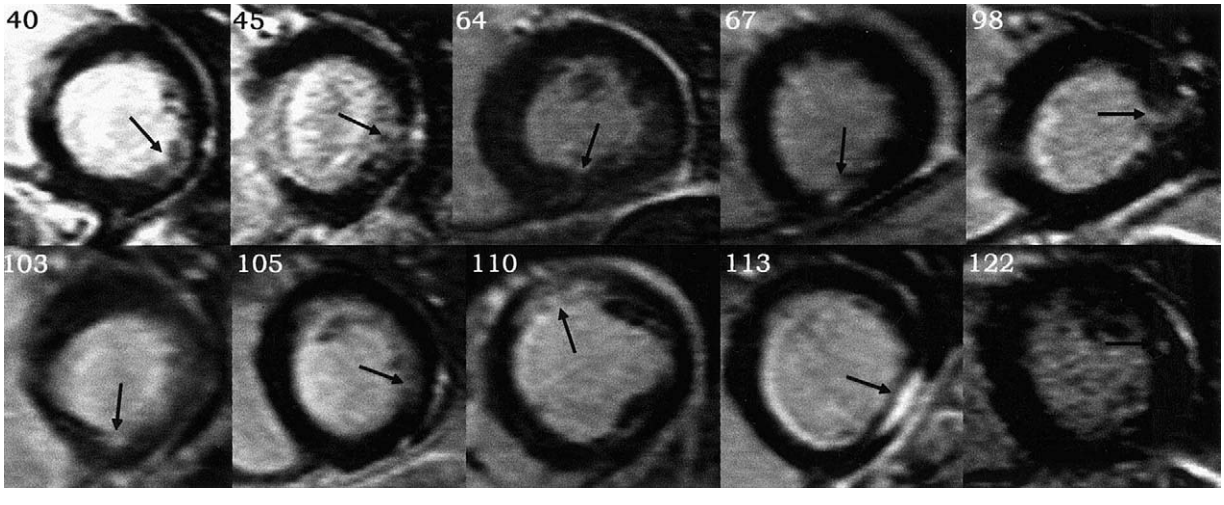

Figure 2. Short-axis magnetic resonance images from 10 consecutive subjects displaying previously unrecognized myocardial infarctions. Note that these myocardial infarction scars were visible in the same location in both short and long axis and that some involve the subendocardial layer in another slice than the one displayed.

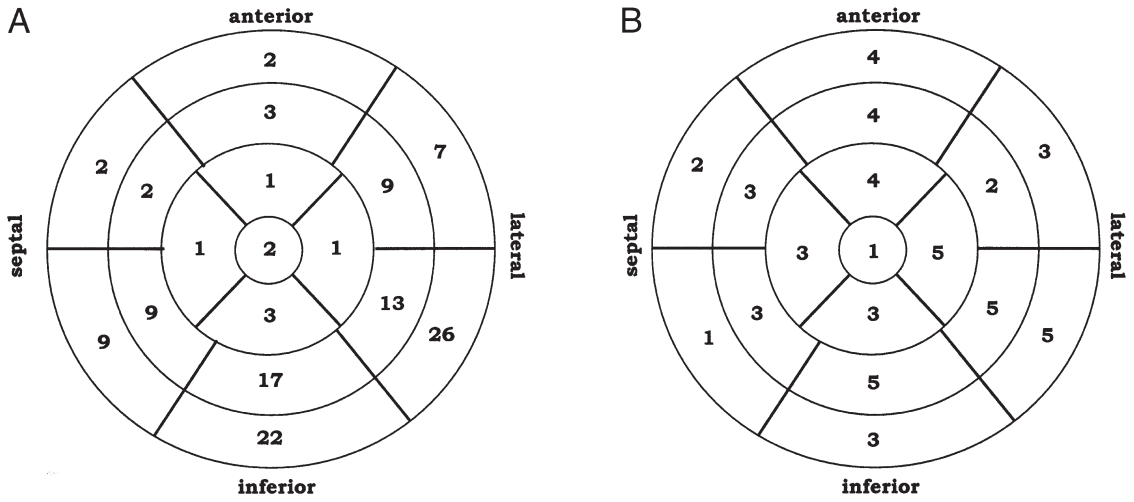

Figure 3. The distribution of unrecognized **(A)** and recognized **(B)** myocardial infarction scars between the 17 segments of the American Heart Association segmentation.

C.E.B. and consensus was 86% and between observer T.B. and consensus was 85%.

DISCUSSION

The present study revealed a greater prevalence of UMI (19.8%) than earlier estimates. The previous estimation tool (i.e., detection of Q waves on ECG) would only have identified 3 of the 49 UMIs that were detected with MRI (Table 2). Furthermore, 7 of the 188 subjects without MI scars had pathological Q waves and would have been classified as having a UMI if ECG had been the tool, proving a discrepancy in the use of the term UMI. However, pathological Q waves are known to occur in other conditions than MIs (16–18), and not all MIs result in pathological Q waves (4), suggesting that ECG is a rather coarse tool for detecting UMIs.

In a previous study of 298 subjects, only 1 UMI was found with MRI (19). However, the investigated population sample in that study consisted of corporation employees with a mean age of 50.2 years, where subjects with known MI, stroke, malignancy, or diabetes were excluded, and only 17% were women (19). The PIVUS population can be regarded as representative of the 70-year-old Swedish population and so can the sample investigated in the present study, since the basic characteristics did not differ significantly (Table 1). However, because the study sample was composed of 70-year-old Caucasians, the results cannot be generalized to other ethnic or age groups.

The subjects received a standardized gadolinium dose suited for whole body MRA. Because cardiac MRI was performed after MRA, the post-contrast times were rather long. It has been claimed, however, that the best contrast between normal and enhanced myocardium in chronic MI

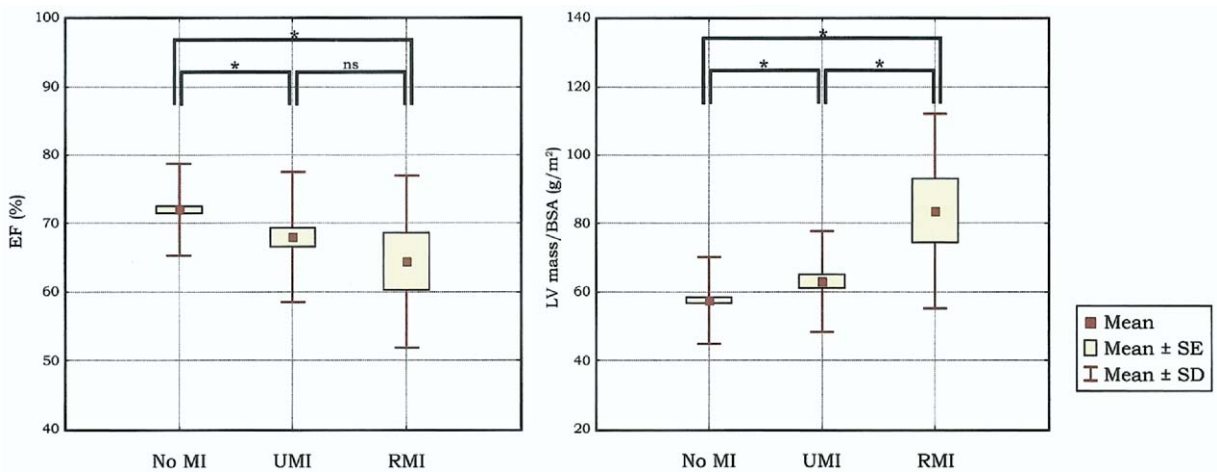

Figure 4. Differences in ejection fraction (EF) and in left ventricular (LV) mass adjusted for body surface area (BSA) and gender between the subjects without myocardial infarction scars (No MI), those with unrecognized myocardial infarction (UMI), and those with recognized myocardial infarction (RMI). *$p < 0.0167$ (i.e., 0.05 with Bonferroni correction).

is seen 25 to 30 min post-contrast (20). Furthermore, the subject imaged at 64 min post-contrast in the present study presented very obvious enhancement.

Animal models have proved late enhancement MRI to be an accurate method for detecting MIs and other myocardial scars (5–7). The infarct size determined with MRI correlates closely to triphenyltetrazolium chloride staining in dogs (21,22), but no such studies have, to our knowledge, been performed in humans. However, MRI infarct size of acute MIs in humans correlates with other indexes of infarct size such as peak troponin I and EF (23).

Interpretation of late enhancement involving the subendocardial layer as representing an MI scar is based on results from a study of 811 cardiac MRI examinations showing that late enhancement in ischemic infarction always involved the subendocardial layer (11). This is supported by findings on comparison of MRI patterns in acute MI and myocarditis (12).

Subendocardial late enhancement is not specific for MI. It can also be present in myocarditis (12), sarcoidosis (11), amyloidosis (24), dilated cardiomyopathy (25), and hypertrophic cardiomyopathy (26). However, in the present study, none of the subjects displaying late enhancement had any of those diagnoses in their medical records before the MRI examination. There is always a possibility that such a disease might be undetected, but because ischemic disease is far more common, particularly in this age group, the late enhancement is more likely to represent MI scars. This is supported by the fact that only 1 UMI was found with MRI in 298 subjects with a mean age of 50 years (19). Furthermore, MI has proved to be one of the most frequently missed clinical diagnoses, in comparisons with autopsy findings (27,28).

Women are said to present with atypical symptoms of MI (29,30), suggesting that their MIs would be unrecognized to a larger extent than MIs in men. In the present study, there was also a larger proportion of women in the UMI group (45%) than in the group with RMI (18%). It has been argued that women get MIs later than men as a result of protective effects of sex hormones in fertile years (29), and ECG detects UMIs in the same proportion as RMIs in men and women (31). However, the prevalence data in the present study suggest that part of the difference may lie in the recognition and not in the actual prevalence of MI.

The fact that the UMIs had significantly smaller volumes than RMIs in this study can explain why UMIs escaped clinical recognition. These UMIs might have been too small to cause any changes on ECG. In addition, MI can present without chest pain and is then frequently unrecognized (32). Only 28.6% of the subjects with UMI in the present study had come to the hospital with chest pain symptoms (Table 2). Furthermore, UMIs were frequently located in the inferolateral segment, where ECG has lower sensitivity than in the anterior and septal segments (4,33).

The clinical impact and prognosis of the UMIs detected with MRI is unknown. However, in the present study, several findings indicate an increased risk in this group. First, cardiac morbidity was more common in subjects with UMI than in those without MI scars (and was even more common in those with RMI) (Table 2), suggesting a possibly worse prognosis. The fact that there was no difference in the prevalence of revascularization between the group without MI scars and the UMI group, but a significant difference between both groups and the RMI group, merely signifies that the RMI group is recognized and, therefore, accessible for treatment. Second, the fact that EF was significantly higher among subjects without MI scars than among those with UMI or RMI indicates that cardiac function may be impaired in those with UMI as well as in those with RMI. Third, LV mass was significantly larger in subjects with UMI than in those without MI scars, and even larger in those with RMI. These observations can endorse the findings, because a larger myocardial mass needs more oxygen than a smaller one. A larger heart would, therefore, be more vulnerable to an impaired blood supply due to atherosclerosis and would more likely become infarcted. A large LV mass is also associated with an increased prevalence of coronary atherosclerosis (34), MI, and a high mortality risk (35–37).

It may be argued that infarctions as small as these UMIs are not clinically relevant. However, the infarct size was probably larger in the acute stage, because it decreases during healing (23,38,39). Furthermore, the fact that the UMI group differed from the group without MI scars in the above 3 parameters suggests a worse prognosis in this group and puts forward the importance of detecting these previously unrecognized MIs.

In conclusion, UMI detected with MRI was more frequent than expected in 70-year-old subjects. The subjects displaying these UMIs may represent a previously unknown potential risk group for future cardiovascular events. The clinical impact and prognosis of these UMIs need to be established by further studies.

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